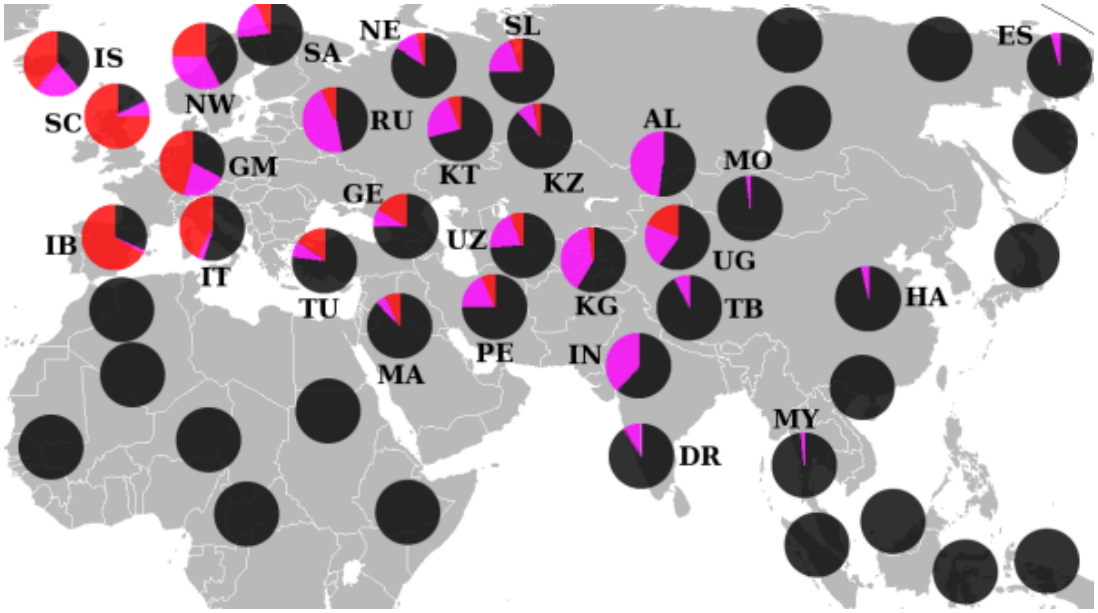
Biology for Physicians: Formal Genetics and Population Genetics

See online here

Mendel's laws, phenotype and genotype, recessive and dominant. Do these terms sound familiar to you from your biology lessons? This article regarding formal genetics will introduce you to all important genetic fundamentals regarding biology that you need to know as a physician. By studying and revising the contents of this article, you will be in a better position to do well both in your preclinical studies as well as in your preliminary exams. This content will help you master the key fundamentals of Genetics.



Genetic Fundamentals

The rules of inheritance had already been established before the mechanisms in both the cellular and molecular level were ever comprehended. It is important that you memorize the following genetic fundamentals well:

- **Allele**: a unit of inheritance that results in a specific trait (original gene (normal allele or "wild type") or mutated gene).
- **Genetic locus**: the location of a gene in the genome.
- **Diploid set of chromosomes**: these are two sets of homologous chromosomes.
- **Genotype**: it is complete genetic information of an organism (entire combination of alleles).
- **Phenotype**: A genetic trait can but does not necessarily have to be expressed in terms of its appearance. This expression is called phenotype.

- **Homozygous**: Both homologous chromosomes have the same alleles.
- **Heterozygous**: Homologous chromosomes have different alleles.
- **Hemizygosity**: Only one copy of a gene is present despite the existence of a diploid set of chromosomes.
- **Polymorphism/multiple alleles**: is the existence of more than two alleles of a gene within a population.

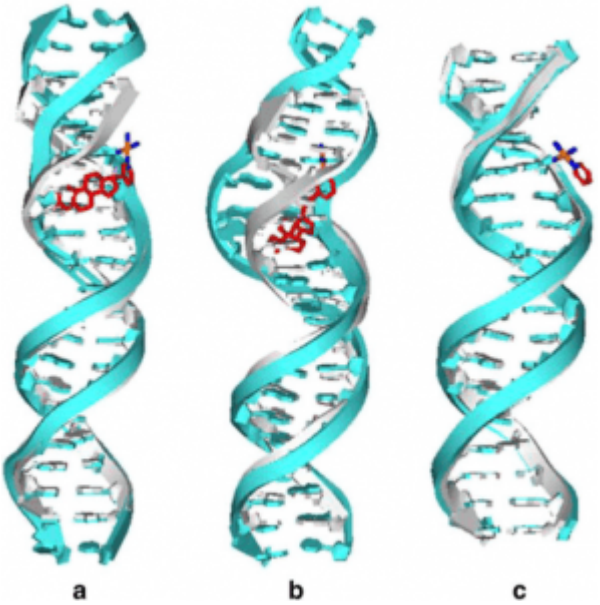


Image: "Disturbance of DNA conformation by the binding of testosterone-based platinum drugs via groove-face and intercalative interactions: a molecular dynamics simulation study" by Openi. License: CC BY 2.0

Types of Inheritance: Dominant, Recessive and Codominant

If an allele is dominant, it is more expressive than the other alleles. A recessive allele, on the other hand, reverts to the phenotype in its effect. Recessive alleles can only manifest in the phenotype of a **homozygous** genotype. **Codominance** means that both alleles are expressed in the phenotype, i.e. blood type AB.

Traits in the phenotype can also be mixed, which is referred to as **intermediate inheritance**, i.e. height. **Expressivity** refers to the degree of expression of a trait. **Penetrance**, on the other hand, refers to the extent to which a trait is present (measured by the proportion of gene carriers).

Conductors are genetic carriers that carry the trait, not in the phenotype but rather recessively in the genotype. Therefore, a conductor can pass on recessive alleles to its descendants without displaying the traits themselves (i.e. red hair). Should a gene control several traits, it is referred to as **pleiotropy**. **Polygenic** traits, on the other hand, are controlled by several genes.

The environmental influence: Phenocopy

The genetic analysis of the origin of a disease becomes difficult if environmental factors are involved; the **phenocopies**.

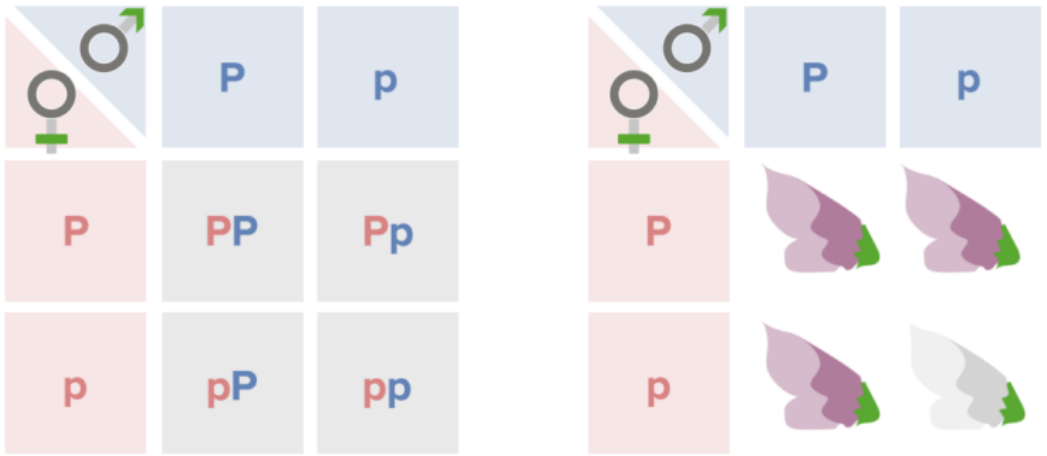
Phenocopies can simulate a genetic cause at first.

Iodine deficiency, for instance, can phenotypically be mistaken for cretinism (genetically determined dwarfism). **Cretinism** is a genetic mutation of the **TSH** or **TRH** hormone. In cases of iodine deficiency, insufficient thyroid hormones are produced. Both cases lead to hypothyroidism.

Genetic Presentation

The Punnett square

The Punnett square, also referred to as **combination square**, was developed by the British geneticist R. Punnett in order to depict the frequency of genotypes in inheritance.



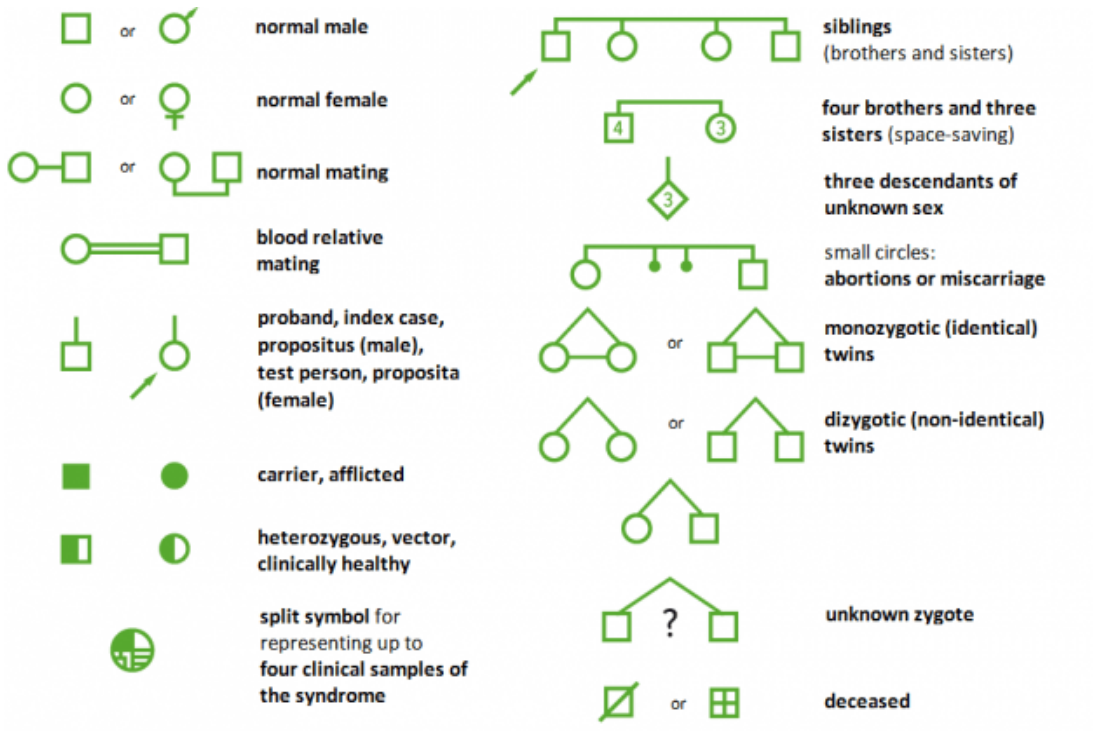
There are 2 possible gametes from each parent. This leads to a 1:2:1 genotypic ratio.	There are 2 possible gametes from each parent. This leads to a 3:1 phenotypic ratio.

Spelling:

- Capital letters: dominant allele
- Both parents are in bold print (example: one part heterozygous Rr and homozygous RR).
- Lower case letters: recessive alleles
- The dominant allele is named first.

Another example can be found in the third Mendel's rule.

Genetic symbols



In our article concerning human genetics, you can read everything regarding **pedigree analysis,** important diseases as well as many interpretation examples.

Mendel’s Laws

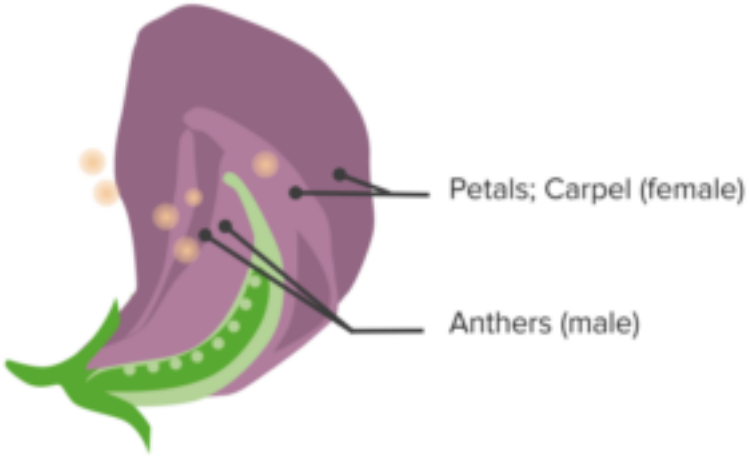
The “father of genetics“ Gregor Mendel (1822 – 1884), an Augustine monk, performed cross-breeding experiments with peas and beans from his monastery’s garden and deduced from them the laws of inheritance that are named after him. In 1865, he presented them for the first time in Bruenn, where his discoveries were initially disregarded by experts. Later, Sutton and Boveri postulated the **chromosome theory** which built on Mendel’s discoveries.

Mendel assumed hereditary factors, which can be passed on by the **parental generation** to the **filial generation**. His derived laws that described the inheritance of uncoupled **autosomal genes** based on statistical laws.

Note: Mendel’s laws are indispensable for the construction and interpretation of pedigrees and the calculation of probabilities.

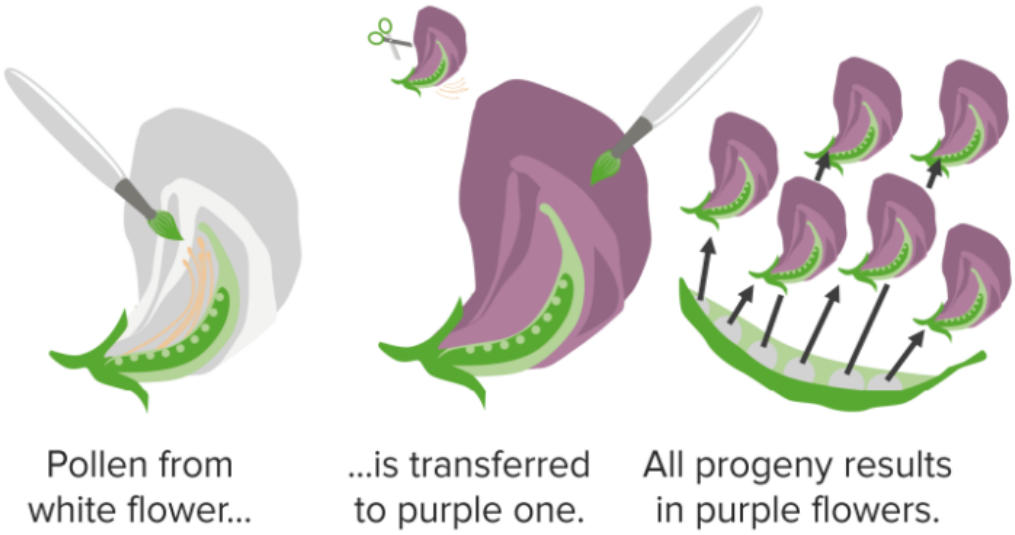
Mendel´s pea plant

Reason for the pea plant



- Many varieties
- Hybrids for previous studies
- Easy to grow
- Short generation time
- Self-fertilization
- Cross-fertilization

The self-fertilization occurs unless altered. Mendel cross-fertilized plants that were true breeding.



First Mendel's law: The principle of uniformity

All descendants (F1 generation) of homozygote parents (P generation) are uniform.

AA × aa = 100 % Aa

P	AA		aa	
F1	**Aa**	**Aa**	**Aa**	**Aa**

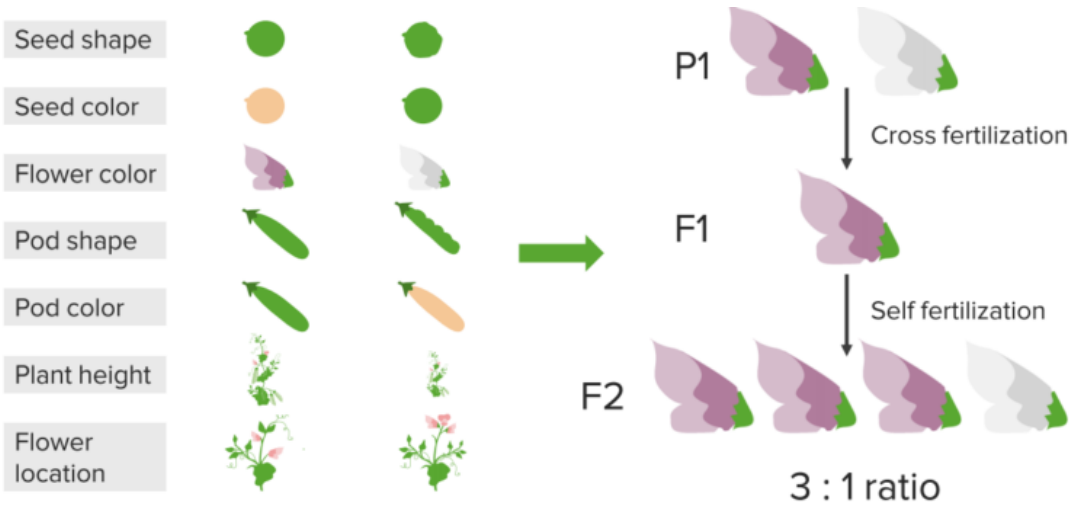
If both homozygous parents carry different alleles of a trait, the F1 generation will be **uniformly heterozygous**. This rule applies independently from the hereditary type (dominant/recessive, codominant or intermediate).

- **Dominant-recessive inheritance**: The dominant allele always dominates in the phenotype (i.e. long stems).

- **Intermediate inheritance**: Both alleles influence one another (i.e. flower colors red and white result in pink in the F1 generation).
- **Codominant inheritance**: Both traits are expressed in the phenotype independently of one another (i.e. blood types AA and BB all have F1 AB).

Second Mendel’s law: The principle of segregation

Mendel chose 7 true breeding traits that exhibited segregation.

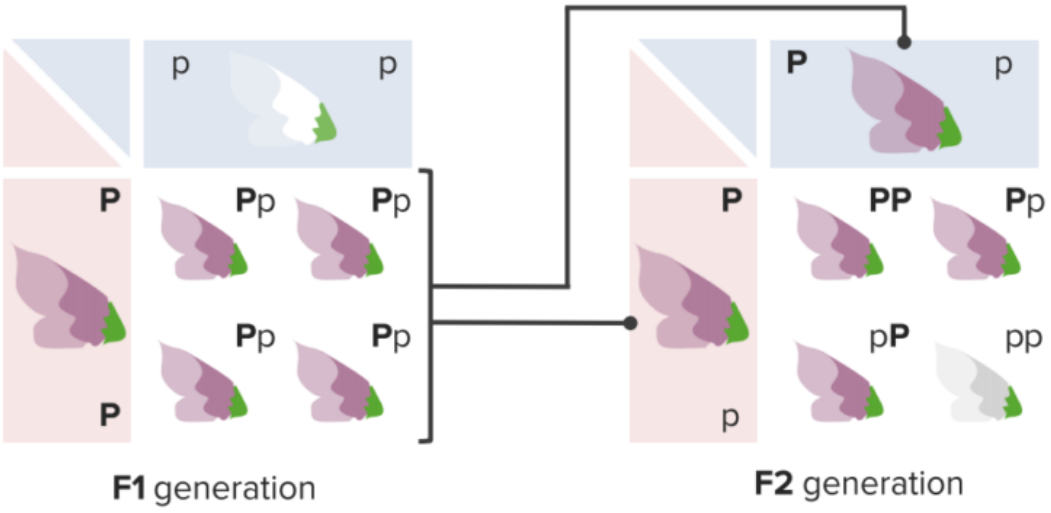


If the heterozygous F1 hybrid generation is crossbred, the F2 generation is split phenotypically according to a certain number ratio (1: 2: 1 or 1 : 3).

Aa × Aa = 25 % aa + 50 % Aa + 25 % AA

F1	Aa		Aa	
F2	**AA**	**Aa**	**Aa**	**aa**

- **Dominant-recessive inheritance**: The recessive inheritance trait reappears in 25 % of descendants. The rest is homozygous for the dominant gene or heterozygous with the appearance of the dominant trait.
- **Intermediate inheritance**: Both original traits of the P generation are homozygous again in 25 % of descendants.

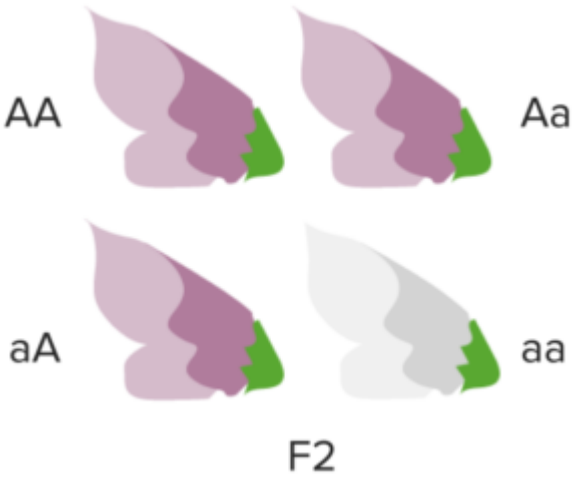


Principle of segregation: alternative alleles for a character segregate from each other during gamete formation and

remain distinct.

Third Mendel’s rule: The principle of independent assortment

So far, Mendel had examined the characteristics of the inheritance of one single trait. After that, he analyzed plants that had two different traits. Here, he also discovered that the F1 generation was identical genotypically as well as phenotypically. If he crossed the F1 hybrids anew, however, new trait combinations appeared in the F2 generation.



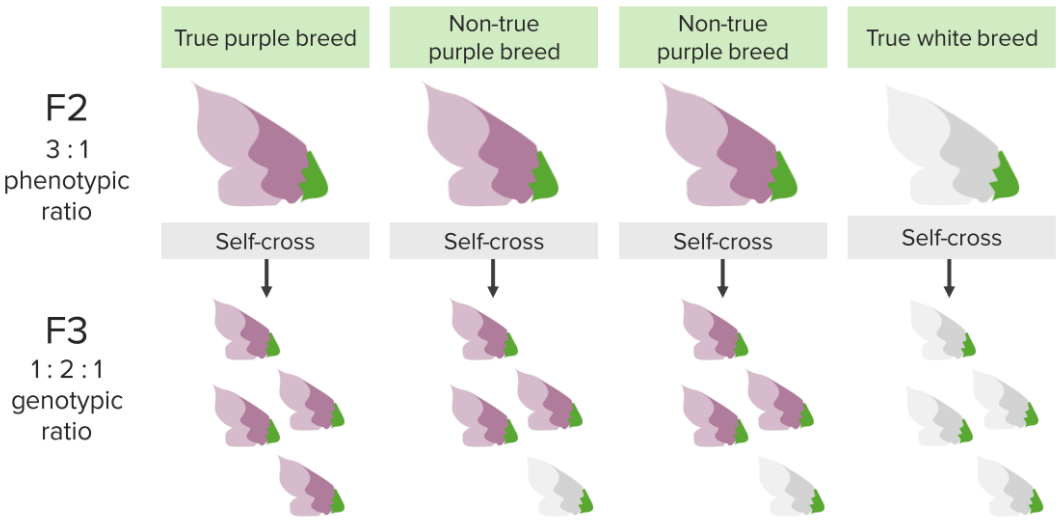
Mendel’s conclusion: The two traits are inherited independently of one another. If individuals, whose genetic makeup differs in several traits, are crossed, the individual traits are inherited independently of each other according to Mendel’s first and second rule.

Self-pollination results in 4 × 4 = 16 allele combinations.

Gametes	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Exception: Neighbouring genes are inherited together as a coupled group. (Therefore, Mendel’s achievements were recognized only posthumously because his discoveries could not be completely verified due to these limitations.)

The following is only applicable to a certain extent as well: The coupled inheritance of allele combinations is interrupted by **crossing-over**. The crossing-over frequency increases in proportion to the distance of two genes within a chromosome.



Examination of One Trait Through Two and Three Generations

Population Genetics

The Hardy-Weinberg law

When studying population genetics, it is not the individual that is the focus but rather the larger groups of individuals that reproduce together. This population provides a common gene pool. The **gene pool** contains several alleles of one gene and the relative proportions of these alleles are termed as **gene frequency**. Gene flow is created when individuals migrate into or away from the population.

In 1908, **Hardy and Weinberg** found (independently of one another):

The frequencies of alleles and genotypes remained constant over generations within a population if the genetic recombination took place according to Mendel's rules without any export out of or import of genes into the existing gene pool. Hence, a mathematical model can be derived via the probability test: the Hardy-Weinberg equation.

The Hardy-Weinberg equation

With the aid of the Hardy-Weinberg equation, population geneticists are able to calculate what percentage of a certain disease is contained in a gene.

If gene A and gene a are distributed in a population which is constant, the following applies:

p + q = 1 or 100%

Gene frequency according to the Hardy-Weinberg equation

The frequencies result from the Punnett square.

- Genotype AA: frequency p^2
- Genotypes Aa, aA: frequency 2pq
- Genotype aa: frequency q^2

Genotype probability	**A**p	**a**q

Ap	**AA**p^2	**Aa**pq
aq	**aA**pq	**aa**q^2

Reference: T. Wenisch (2013): mediscript Kurzlehrbuch Biologie, S. 94, Tab. 2.4. Elsevier Verlag.

The Hardy-Weinberg equation: $p^2 + 2pq + q^2 = 1$

The Hardy-Weinberg applies if:

- a purely coincidental pairing of individuals in the population occurs.
- there are no selection effects (favoring certain genotypes).
- there is no gene flow and/or mutation in the gene pool.
- the population is large enough that the probabilities are equal to the frequencies.

These prerequisites only apply to a shorter observation period. Changes in the gene pool always occur over longer periods of time.

Sample calculation

Question: In a population, the dominant allele is present with a frequency of 60% in the gene pool. How does the distribution of the possible genotypes within the population look like?

p = 60%, q = 40%, because q + p = 100%

$(0,6)^2 + 2 \times (0,6 \times 0,4) + (0,4)^2 = 1$

0,36 + 0,48 + 0,16 = 1

p^2 = 36%, pq = 48%, q^2 = 16

Answer: 36% are AA, 48% are Aa, 16% are aa.

Selection and coincidence

Over longer periods of time, the gene pool of a population always changes: Genes are imported or change due to coincidental new mutations. Natural selection favour individuals with a genetic composition that secures the survival and reproduction chances or even increases them. Their genes will occupy a growing share of the gene pool over a longer period of time.

If the genes that offer survival advantages are dominant, they spread rapidly. On the other hand, dominant genes that are disadvantageous to the individual, disappear quickly. Recessive genes remain longer in a population.

Sickle cell anemia: Selective advantages through gene defects

Sickle cell anemia is an example of a regionally frequent gene defect, which offers its carriers a selective advantage. Sickle cell anemia, a **hemolytic anemia**, is especially prevalent among black Africans. Heterozygous carriers, who carry the **HbS gene**, have a higher resistance to malaria than non-carriers. Thus, through their selective advantages, the conductors in malaria-endemic regions receive a high share of the HbS gene in the gene pool of the population.

Tay-Sachs disease: The founder effect

If a smaller group isolates itself from a population, splits off and reproduces, a **genetic drift** is more than likely to occur. If a genetic drift develops in a new colony, it is referred to as a **founder effect**. Tay-Sachs disease is an example of a founder effect: This disease is especially common among Ashkenazic Jews in the USA.

Genetic Polymorphisms

You have already come across the term polymorphism under genetic fundamentals. Genetic polymorphisms are categorized in the “normal“ range. Various alleles mutate incidentally and cannot be considered as pathological. If these varying genotypes occur frequently, however, they are referred to as polymorphisms.

Proteins and enzymes are not functional in all variables but rather only in certain configurations. An enzyme/protein polymorphism exists if the polymorphism is of consequence in the genome as well, meaning the gene products can thus be differentiated, i.e. in an enzyme.

The combination possibilities of the variables mean biochemical individuality for every human being.

Every human being can be identified through the “genetic fingerprint.”

The only exception is in identical twins: They have an identical genome.

Uniparental Disomy

In uniparental disomy, both chromosomes of a homologous chromosome pair come from one parent. This leads to a disruption of **genomic imprinting**. One should differentiate between its two forms:

- **Paternal uniparental disomy**: The maternal chromosome and its genes are missing.
- **Maternal uniparental disomy**: The paternal chromosome and its genes are missing.

Failure of genetic expression or overexpression of genomic imprinting can lead to certain diseases, i.e. **Prader-Willi syndrome** or **Angelman syndrome**.

The disruption of imprinting caused by uniparental disomy is not passed on to the next generation. The expression of genetic information takes place anew and there is no increased risk of recurrence in families.

Review Questions

The answers can be found below the references.

1. In a population, every fiftieth individual is heterozygous for an allele resulting in phenylketonuria in homozygotes. How high is the frequency of this disease in this particular population?

A. 1 : 100
B. 1 : 2,500

C. 1 : 5,000
D. 1 : 10,000
E. 1 : 100,000

2. In families with two children, both parents are heterozygous for the same gene. This gene causes an anomaly in homozygotes. How high is the expected share of families in which both children have this anomaly?

A. 1 / 25
B. 1 / 16
C. 1 / 8
D. 1 / 4
E. 1 / 2

3. Which disease is caused by uniparental disomy; a disruption of genomic imprinting?

A. Prader-Willi syndrome
B. Down syndrome
C. Arnold-Chiari malformation
D. DiGeorge syndrome
E. Duchenne muscular dystrophy

References

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Correct Answers: 1D, 2B, 3A

Notes